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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,637	02/06/2007	Dieter Scheller	6102-000034/US/NP	2828

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EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
09/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,637	SCHELLER ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/29/2009* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-20* is/are pending in the application.

4a) Of the above claim(s) *15-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-14 and 19-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. The amendments filed 6/29/2009 were entered.

Response to Arguments

2. Applicants' arguments, filed 6/29/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn and Applicant's arguments as to withdrawn rejections are rendered moot. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

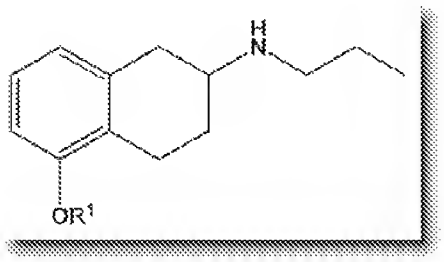
Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. **Claims 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over *van Vliet et al* (cited in a previous Action) in further view of *Wikstrom et al* (cited in a previous Action) and *Rodenhuis* (cited in a previous Action).**

6. Instant **claims 19-20** are drawn to a compound having the formula 

in the (S)-configuration that, when administered to a human body, is cleaved, processed or metabolized to (S)-2-N-propylamino-5-hydroxytetralin.

7. *van Vliet et al* teach the dopaminergic racemic compound **2-N-propylamino-5-hydroxytetralin** (Table 1, Compound 11). More specifically, *van Vliet et al* disclose that the affinity of racemic 2-N-propylamino-5-hydroxytetralin for the dopamine receptor subtypes D_{2L}, D_3 and $D_{4.2}$ (based on antagonist competition binding studies using ^{3}H-spiperone) is 285, 0.75 and 76 (K_i nM) respectively (Table 2, Compound 11) seemingly indicating good selectivity for D_3 versus D_{2L}. However, as noted by *van Vliet et al*, the D_2 receptor can exist in a high- **or** low-affinity state for agonists (Page 4234, Column 2) and the affinity of racemic 2-N-propylamino-5-hydroxytetralin for the **high**-affinity D_{2L} receptor (based on agonist competition binding studies using ^{3}H-N-0437) is 0.50 (K_i nM) (Table 2, Compound 11). Accordingly, *van Vliet et al* teach that racemic 2-N-propylamino-5-hydroxytetralin (albeit ***not*** a highly selective D_3 receptor agonist) is a potent high-affinity D_{2L}/D_3 receptor agonist. In fact, 2-N-propylamino-5-hydroxytetralin appears to be the most potent D_{2L}/D_3 receptor agonist tested by *van Vliet et al* (Page 4236, Table 2). For at least this reason, the skilled artisan would have found it *prima facie*

obvious to formulate potent high-affinity D_{2L}/D_3 receptor agonist compositions specifically comprising 2-N-propylamino-5-hydroxytetralin in view of *van Vliet et al* with a reasonable expectation of success.

8. However, *van Vliet et al* do not teach the (S) enantiomer of 2-N-propylamino-5-hydroxytetralin, nor do they teach a prodrug thereof. Yet, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of *van Vliet et al* with the teachings of *Wikstrom et al*. *Wikstrom et al* teach enantiomeric separation of related aminotetralins to increase dopamine agonistic activity. Specifically, *Wikstrom et al* investigated the potency of enantiomers of the structurally and functionally related compound 5-hydroxy-2-(N,N-di-n-propylamino)tetralin (5-OH-DPAT) which "have been classified as less potent in the previous studies" (Page 217, Column 1, Paragraph 3). Significantly, *Wikstrom et al* report that the (S) enantiomer of the compound, having an ED_{50} of 3.7 nmol/kg, was significantly more potent than the racemic compound (Page 219, Table III, compound 1(S)) having an ED_{50} of 11 nmol/kg (Page 219, Column 2, Paragraph 6). Accordingly, one of ordinary skill in the art at the time the invention was made would have been motivated to subject 2-N-propylamino-5-hydroxytetralin to enantiomeric separation, and would have been especially motivated to select the (S) enantiomer of the compound.

9. Furthermore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to formulate suitable prodrugs of (S) 2-N-propylamino-5-hydroxytetralin in light of *Rodenhuis*. *Rodenhuis* teaches that hydroxylated 2-aminotetralins "display limited activity upon oral administration. A major disadvantage of the hydroxylated 2-aminotetralins and other phenolic compounds is that they undergo considerable inactivation by

glucuronidation in the gut and the liver. One of the strategies to circumvent the problem of the low oral bioavailability of the hydroxylated 2-aminotetralins is to search for suitable prodrugs. Frequently investigated prodrugs of phenols are esters and carbamates" (Page 98, Chapter 6, Introduction, Paragraph 3). Thus, one of ordinary skill in the art would have been motivated to formulate prodrugs of (S) 2-N-propylamino-5-hydroxytetralin which would necessarily be cleaved, processed or metabolized to 2-N-propylamino-5-hydroxytetralin upon administration to a human body, as recited by claim 19. Accordingly, claims 19-20 are rejected as *prima facie* obvious.

10. Applicant, however, argues that it would have been unexpected that (S) 2-N-propylamino-5-hydroxytetralin prodrugs would be purely agonistic and have a strongly pronounced functional D_3 selectivity (Applicant Argument, Pages 10-11). In the instant case, Applicant discloses that (S) 2-N-propylamino-5-hydroxytetralin has an IC_{50} for D_3 of 7.6 compared to 290 for D_2 (K_i nM) (Page 4, Table 1) "measured using competition experiments" (Specification, Page 12, Paragraph 0070). Yet, it is unclear ***which*** competition experiments were used to measure the receptor affinity in the instant case. For example, as discussed above, *van Vliet et al* disclose that the affinity of racemic 2-N-propylamino-5-hydroxytetralin for the dopamine receptor subtypes D_{2L} and D_3 is 285 and 0.75 (K_i nM) respectively (based on antagonist competition binding studies using ^{3}H-spiperone); but only 0.50 and 0.75 (K_i nM) (based on agonist competition binding studies including ^{3}H-N-0437 which is specific for the affinity for the high-affinity D_{2L} receptor) (*see* Table 2, Compound 11). Since it is unclear which competition experiments were used to measure the receptor affinity in the instant case, the results can not be considered unexpected.

11. Thus, for all the foregoing reasons, instant claims 19-20 are rejected as *prima facie* obvious.

12. **Claims 10-14 are is rejected under 35 U.S.C. 103(a) as being unpatentable over *van Vliet et al* in further view of *Wikstrom et al* and *Rodenhuis* as applied to claim 19 above, in further view of *den Daas et al* (cited in a previous Action)**.

13. Instant claims 10-12 and 14 are drawn to compositions containing (S) 2-N-propylamino-5-hydroxytetralin or a prodrug thereof **and a pharmaceutically acceptable carrier or adjuvant**. More specifically, wherein the composition is adapted for transdermal, transmucosal or parenteral administration, as recited by instant claim 13.

14. As discussed above, *van Vliet et al* in further view of *Wikstrom et al* and *Rodenhuis* teach (S) 2-N-propylamino-5-hydroxytetralin and prodrugs thereof. However, none of the prior art teach the *prima facie* obvious composition further comprising a pharmaceutically acceptable carrier or adjuvant, or wherein the composition is adapted for transdermal, transmucosal or parenteral administration.

15. As discussed in the previous Action, *Rodenhuis* teaches that hydroxylated 2-aminotetralins "display limited activity upon oral administration" and suggest formulating prodrugs to overcome this problem (Page 98, Chapter 6, Introduction, Paragraph 3). In addition, *den Daas et al* teach "[a]nother possibility to avoid first-pass metabolism is the administration of compounds via the transdermal route" (Page 655, Column 2, Second Paragraph). Thus, noting that "[t]he next logical step in the transdermal application of dopamine agonists would be the use of transdermally applicated prodrugs" (Page 655, Column 2, Third Paragraph), *den Daas et al* teach compositions comprising structurally and functionally related compounds and further

comprising a pharmaceutically acceptable carrier or adjuvant, wherein the composition is adapted for transdermal, transmucosal or parenteral administration (Page 656, Column 1, First Paragraph). Accordingly, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to formulate the *prima facie* compositions taught by *van Vliet et al* in further view of *Wikstrom et al* and *Rodenhuis* with a pharmaceutically acceptable carrier or adjuvant, wherein the composition is adapted for transdermal delivery in view of *den Daas et al*. The skilled artisan would have been motivated to do so in order to avoid the risk of metabolic inactivation with a reasonable expectation of success.

16. Accordingly, instant claims 10-14 are rejected as *prima facie* obvious.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CRAIG RICCI/
Examiner, Art Unit 1614

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